

Mixed Quantum Mechanical/Molecular Mechanical (QM/MM) Simulations of Adiabatic and Nonadiabatic Ultrafast Phenomena

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Abstract: A thorough theoretical description of ultrafast phenomena that occur in complex systems constitutes a formidable challenge. It not only necessitates the use of quantum mechanical methods that can describe ground and possibly even electronically excited state potential energy surfaces with sufficient accuracy but also calls for approaches that can take the real-time dynamics of a system and the coupling between its electronic and nuclear degrees of freedom fully into account. Over the last years, our group has been active in the development of mixed quantum mechanical/molecular mechanical (QM/MM) methods for the *in situ* simulations of dynamical phenomena in ground^[1] and excited^[2] states within the adiabatic (Born-Oppenheimer) approximation. Recently, we have extended our theoretical tools with the explicit inclusion of nonadiabatic effects in the framework of Ehrenfest dynamics and Tully's fewest switches surface hopping. These extensions allow the theoretical description of nonadiabatic ultrafast phenomena in the gas phase as well as in solution, and complex biological environments.

Keywords: Excited states · *First-principles* molecular dynamics · Nonadiabatic dynamics · QM/MM simulations · Rhodopsin · Time-dependent density functional theory

Introduction

First-principles molecular dynamics has become a very successful and widespread method for the study of chemical reactions that occur in the electronic ground state. In particular, *ab initio* Born-Oppenheimer (BO) and Car-Parrinello (CP) dynamics^[3] are the most popular approaches designed for the computation of classical nuclear trajectories using forces derived at a quantum mechanical level. Due to the prohibitively high computational costs of a conventional quantum chemical calculation based on the many-electron wavefunction, the potential

energy surfaces governing the nuclear dynamics are usually computed using the density functional (DFT) formulation of the electronic Schrödinger equation. In this way, electronic energies and their nuclear gradients (forces) are expressed as simple functional of the total electronic density.

More recently, Runge and Gross^[4] proposed an extension of DFT for the case of a system of electrons under the influence of a time-dependent external field. This development, named time-dependent density functional theory (TDDFT), has opened a new avenue for *first-principles* studies of the dynamics of molecular systems in electronically excited states since it offers a computationally affordable way for the calculation of excited potential energy surfaces (PESs) as a functional solely of the ground state density (or equivalently of the corresponding Kohn-Sham orbitals). However, the combination of standard ground state *ab initio* molecular dynamics techniques with TDDFT energies and forces^[5,6] turned out to be more involved than expected. In fact, excited state dynamics cannot be fully described without including nonadiabatic effects derived from the quantum nature of the nuclear degrees of freedom. The breakdown of the BO approximation increases dramatically the degree of complexity of the problem, since a single trajectory is in general not sufficient for an accurate description of the coupled dynamics of electrons and nuclei (with the

exception of mean field solutions based on the Ehrenfest theorem). In addition, non-adiabatic couplings (NACs) are naturally defined in terms of electronic wavefunctions, and therefore a density functional representation of these quantities is required for the design of an *ab initio* excited state molecular dynamics approach based on TDDFT PESs.

We have recently developed the theoretical foundations for the calculations of NACs within a TDDFT framework and have implemented Ehrenfest and surface hopping dynamics in combination with mixed quantum mechanical/molecular mechanical (QM/MM) simulations enabling the simulation of nonadiabatic processes in complex systems.

Methods

Ehrenfest dynamics

The first step in the derivation of mixed quantum-classical dynamics consists in the formulation of an *Ansatz* for the representation of the wavefunction of the total system. Depending on this choice, different approximate mixed quantum-classical equations of motion can be obtained, for instance, the so-called Ehrenfest dynamics, which makes use of a simple factorization of the total wavefunction into the product of a fast electronic and a slow nuclear part, according to Eqn. (1)

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$$\Psi(\mathbf{r}, \mathbf{R}, t) = \Phi(\mathbf{r}, \mathbf{R})\Omega(\mathbf{R}, t)e^{\frac{i}{\hbar} \int_0^t dt' E_{ch}(t')}, \quad (1)$$

where the phase factor is

$$E_{ch}(t) = \int \int d\mathbf{r} d\mathbf{R} \Phi^*(\mathbf{r}, \mathbf{R})\Omega^*(\mathbf{R}, t) \hat{H}_{el}(\mathbf{r}; \mathbf{R})\Phi(\mathbf{r}, \mathbf{R})\Omega(\mathbf{R}, t) \quad (2)$$

and $H_{el}(\mathbf{r}; \mathbf{R})$ is the electronic Hamiltonian that depends parametrically on the nuclear positions. The coupling with an external time-dependent potential can be included through the coupling with the electrostatic vector potential $\mathbf{A}(\mathbf{r}, t)$.^[7]

Trajectory Surface Hopping Dynamics

Recently we have developed a trajectory surface-hopping AIMD scheme based on TDDFT.^[8] All relevant quantities, namely ground- and excited-state energies, nuclear forces,^[5,6] nonadiabatic couplings,^[9–11] and transition dipole elements are expressed as a functional of the electronic density or, equivalently, of the Kohn-Sham (KS) orbitals, in the framework of linear-response time-dependent density functional theory (LR-TDDFT).^[12]

Tully's surface hopping differential equations^[13] that govern the dynamics of the nuclei are obtained by replacing

$$\Psi^\alpha(\mathbf{r}, \mathbf{R}, t) = \sum_J C_J^\alpha(t)\Phi_J(\mathbf{r}; \mathbf{R}) \quad (3)$$

in the time-dependent Schrödinger equation for the combined electron-nuclear system, which gives

$$i\hbar\dot{C}_J^\alpha(t) = \sum_I C_I^\alpha(t)(H_{JI} - i\hbar\dot{\mathbf{R}}^\alpha \cdot \mathbf{d}_{JI}^\alpha), \quad (4)$$

where the label α indicates that the corresponding quantities are evaluated for the trajectory α of the ensemble of trajectories. Because of the adiabatic representation of the electronic wave functions, the matrix elements H_{JI} are diagonal $H_{JI} = \delta_{JI}E_J^{\text{el}}(\mathbf{R})$, where $E_J^{\text{el}}(\mathbf{R})$ are the excited state energies computed using TDDFT equations. In Tully's surface hopping dynamics, the classical trajectories evolve adiabatically according to BO dynamics until a hop between two potential energy surfaces (H_{II} and H_{JJ}) occurs with a probability given by a Monte Carlo-type criterion. In the 'fewest switches' algorithm, the transition probability from state I to state J in the time interval $[t, t + dt]$ is

$$g_{IJ}^\alpha(t, t + dt) \approx 2 \int_t^{t+dt} d\tau \frac{\text{Im}[C_J^\alpha(\tau)C_I^{\alpha*}(\tau)H_{JI}(\tau)] - \text{Re}[C_J^\alpha(\tau)C_I^{\alpha*}(\tau)\Xi_{JI}^\alpha(\tau)]}{C_I^\alpha(\tau)C_I^{\alpha*}(\tau)}, \quad (5)$$

where

$$\Xi_{JI}^\alpha(\tau) = \dot{\mathbf{R}}^\alpha \cdot \mathbf{d}_{JI}^\alpha(\tau), \quad (6)$$

and a hop occurs if and only if

$$\sum_{K \leq J-1} g_{IK}^\alpha < \zeta < \sum_{K \leq J} g_{IK}^\alpha, \quad (7)$$

where ζ is generated randomly in the interval $[0, 1]$. In practice, a swarm of trajectories is propagated independently starting from different initial conditions, and the final statistical distribution of all these trajectories is assumed to reproduce the correct time evolution of the nuclear wavepacket. It is important to stress that, at present, no formal justification of Tully's algorithm has been formulated.

For this reason, we are currently developing a formally exact trajectory-based solution of the combined electron-nuclear time-dependent Schrödinger equation.^[14] The method named NonAdiabatic Bohmian Dynamics (NABDY) is based on quantum trajectories that can be propagated on-the-fly using DFT and LR-TDDFT.

Recently, we have also developed an extension of Tully's trajectory surface hopping scheme to couple nuclear and electronic degrees of freedom with an external electromagnetic field.^[15] The resulting numerical algorithm allows for a more realistic description of the photoexcitation process that was previously approximated by an *ad hoc* vertical excitation of the system into one of its excited states at the beginning of the simulation.

In this formalism, the coupling with the field is added in the normal expression for the $C(t)$ coefficients (Eqn. (4)) of trajectory surface hopping:

$$i\hbar\dot{C}_J^\alpha(t) = \sum_I C_I^\alpha(t)(H_{JI} - i\hbar\dot{\mathbf{R}}^\alpha \cdot \mathbf{d}_{JI}^\alpha + i\omega_{JI} \frac{A_0}{c} \boldsymbol{\epsilon}^\lambda \cdot \boldsymbol{\mu}_{JI}^\alpha e^{-i\omega t}) \quad (8)$$

where A_0 is here the vector potential strength, ω_{JI} is the energy difference between the electronic states J and I, ω is the frequency of the external field, $\boldsymbol{\mu}_{JI}^\alpha$ is the position dipole vector between states I and J, and $\boldsymbol{\epsilon}^\lambda$ is the polarization vector. The usual trajectory surface hopping probability is modified according to Eqn. (8).

As a result of the coupling with the external electric field, population is transferred according to the polarization and frequency of the external field. The excitation of the molecular system corresponds

to a 'hop' from the ground to the excited state and happens when the accumulated amplitude in the target state induces a sufficiently large probability to trigger the transition (see Eqn. (5)).

Applications

In the following, we briefly report some applications of the trajectory surface hopping scheme described above. These examples well illustrate the possibilities offered by this approach in the study of ultrafast photochemical and photophysical processes in the gas phase and in complex environments (modeled at a classical molecular mechanical level). The time and spatial resolution of our simulations offer an almost unique opportunity for the direct observation of photoinduced processes at atomistic resolution, and thus provide theoretical support for a mechanistic interpretation of experiments in ultrafast spectroscopy.

Photodynamics of Oxirane

The efficiency of our implementation has been tested with small molecules. We present here the case of oxirane (ethylene oxide), which has been coupled to a train of ultrashort Π -pulses depicted at the bottom of Fig. 1. The population of a specific trajectory running on the ground state surface is rapidly spread among the different electronically excited states (Fig. 1, upper panel), resulting in several electronic transitions (mid panel, Fig. 1). Interestingly, a longer permanence on the first electronic state produces, after 200 fs of irradiation, C–O bond dissociation of the molecule. Note finally that an extended statistical study of this phenomena requires a large number of independent trajectories.

Nonadiabatic Relaxation of $[\text{Ru}(\text{bpy})_3]^{2+}$ in Aqueous Solution

An environmental effect that needs to be included in a realistic description of many ultrafast nonadiabatic phenomena is solvation. In a recent work,^[16] we have extended the gas phase trajectory surface hopping (THS) to a QM/MM formalism. Solvent effects are therefore incorporated through classical molecular mechanics, whereas the molecule of interest is described at a quantum mechanical level (using DFT for the ground state and LR-TDDFT for the excited states).

Using this LR-TDDFT/MMTSH methodology, we have studied the nonadiabatic relaxation of ruthenium(II)tris(bipyridine) ($[\text{Ru}(\text{bpy})_3]^{2+}$) in water (Fig. 2). Ultrafast experiments have shown^[17] that $[\text{Ru}(\text{bpy})_3]^{2+}$, after photoexcitation into a singlet metal to ligand charge transfer

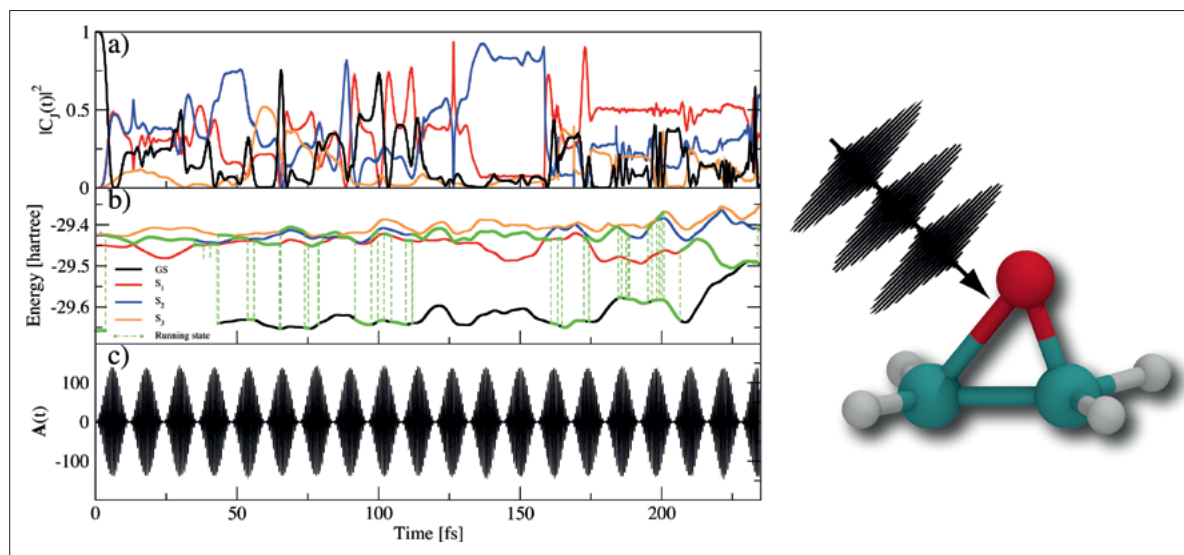


Fig. 1. Oxirane under an electromagnetic field. Upper panel shows the time evolution of the population of a selected independent trajectory. Mid panel presents the different potential energy curves along the dynamics, where the green (dashed) line indicates the driving state. Lower panel depicts the train of ultrashort pulses applied on oxirane (represented on the right).

(¹MLCT) state, undergoes intersystem crossing to a ³MLCT state within 100 fs. The dynamics of this complex in the ground state and in the long-lived triplet state was extensively studied in previous works,^[18,19] whereas the mechanism of nonadiabatic relaxation from the initially populated ¹MLCT states is still unknown. Starting from the first ¹MLCT state with large oscillator strength, our calculations corroborate the experimental findings by first showing a very fast nonadiabatic relaxation among several ¹MLCT states of [Ru(bpy)₃]²⁺. In addition, after a few tens of femtoseconds, important crossings and couplings with ³MLCT states are observed, according to a qualitative analysis of the spin-orbit coupling matrix elements. This indicates that several intersystem crossing events can already take place after 50 fs of dynamics. Even though the time scale

of such nonradiative relaxations does not allow large molecular rearrangement, fast rotations of water molecules occur in the second coordination sphere and may lead to a stabilization of the excited states.

Signal Transduction upon Ultrafast *cis-trans* Photoisomerization in Rhodopsin

Rhodopsin is a member of the G-protein coupled receptor (GPCR) family^[20,21] responsible for light-detection and is the main player of an extremely efficient and ultrafast process. Unlike other GPCRs,^[22] the activation pathway of rhodopsin has been elucidated by spectroscopic experiments as well as X-ray crystallography: in the dark state, the binding site of rhodopsin is occupied by the inverse agonist 11-*cis* retinal, which is covalently linked to residue K296 of transmembrane helix 7 *via* a protonated Schiff base. Photo-induced isomerization (quantum yield: 0.67) of the chromophore from 11-*cis* to all-*trans* inside the binding pocket leads to a cascade of fast conformational changes that ultimately lead to receptor activation and downstream signaling, through the destabilization of some crucial cytoplasmatic interactions.^[23]

Using molecular dynamics, we have been able to follow the real time evolution of a membrane-embedded rhodopsin dimer (Fig. 3, left panel) after photoisomerization up to the microsecond time scale. In this way, we were able to structurally characterize all of the distinct intermediates of the photocycle (Fig. 3, right panel) that have been previously proposed by infrared and Raman spectroscopy: photorhodopsin (occurring *ca.* 200 fs after photoisomerization), Bathorhodopsin (picoseconds), Blue Shifted Intermediate (BSI), Lumirhodopsin (nanoseconds),^[24] Metarhodopsin I (microseconds), and Metarhodopsin II (milliseconds).^[25]

In addition, these simulations have rationalized the experimentally observed enhanced activation efficiency of dimeric rhodopsin with respect to the monomeric form,^[26] indicating that the dimer interface plays a crucial role in this process. In fact, the signal is transmitted through the dimer interface from one monomer to the other within a few tens of nanoseconds following photoexcitation. Through this asymmetric mechanism, the relaxation of the photoexcited chromophore in one monomer is directly relayed to the other subunit that undergoes conformational rearrange-

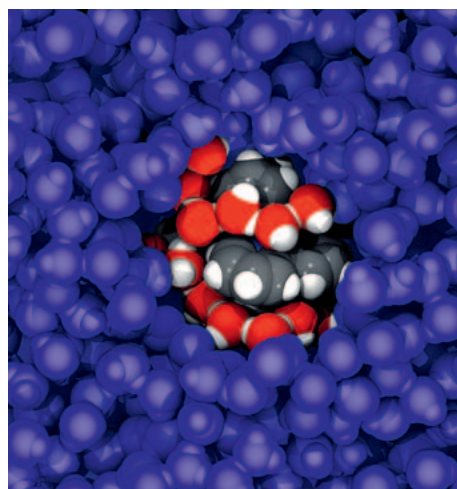


Fig. 2. Ruthenium (II) tris(bipyridine) (QM) surrounded by classical water molecules. Atoms of the closest water molecules are shown in red (oxygens) and white (hydrogens). Further solvation water molecules are shown in dark blue.

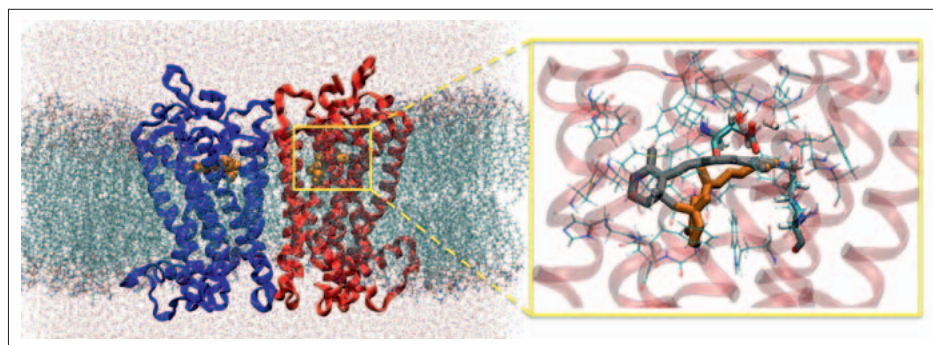


Fig. 3. Left panel: rhodopsin dimer model immersed in a lipid bilayer with explicit solvent. Right panel: outline of the rhodopsin binding pocket and of the protonated Schiff Base conformation in the dark (orange) and batho (grey) photointermediates.

ments towards the active state for G-protein coupling, suggesting that dimerization could be a possible regulatory mechanism for adaptive light detection.

Conclusion and Outlook

Our preceding and continued efforts in the development and application of more and more powerful tools for the computational description of ultrafast phenomena provide direct theoretical support for the experimental investigations within the NCCR MUST while quantitative experimental data serves in turn to validate and assess the performance of different theoretical methods.

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